ROYAUME DE BELGIQUE

MINISTERE DES AFFAIRES ECONOMIQUES
ADMINISTRATION DE LA POLITIQUE COMMERCIALE

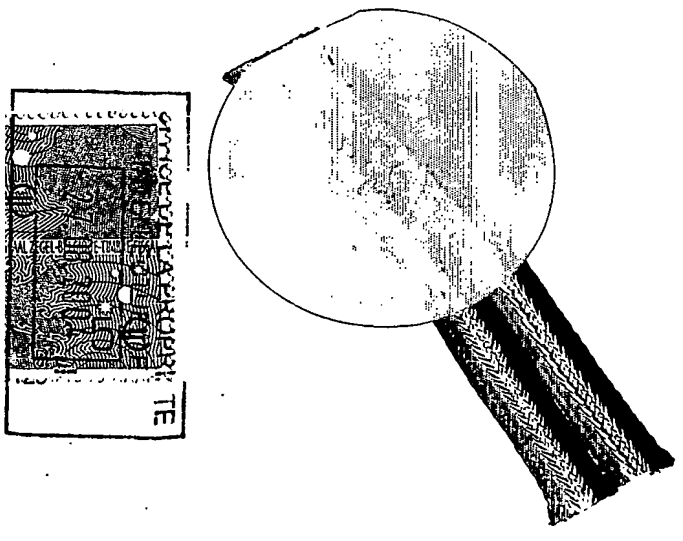
Il est certifié que les annexes à la présente sont la copie fidèle de documents que détient l'Office de la Propriété Industrielle.

Bruxelles, le 27. -8- 2004

Pour le Conseiller de l'Office
de la Propriété industrielle

Le fonctionnaire délégué,

BAILLEUX G.
Conseiller adjoint



PRIORITY DOCUMENT
SUBMITTED OR TRANSMITTED IN
COMPLIANCE WITH
RULE 17.1(a) OR (b)

PCT

REQUEST

The undersigned requests that the present international application be processed according to the Patent Cooperation Treaty.

For receiving Office use only

International Application No. PCT/BE03/00132

International Filing Date 05 AOU 2003 (05-08-2003)

RO/BE - INTERNATIONAL APPLICATION
Name of receiving Office and "PCT International Application"

Applicant's or agent's file reference *(if desired) (12 characters maximum)* RP/PCT/03-14

Box No. I TITLE OF INVENTION

New single unit pharmaceutical composition comprising a mixture of a fibrate and an homocysteine reducing agent

Box No. II APPLICANT ☐ This person is also inventor

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)*

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Applicant's registration No. with the Office

State *(that is, country)* of nationality: BE

State *(that is, country)* of residence: BE

This person is applicant for the purposes of: ☐ all designated States ☒ all designated States except the United States of America ☐ the United States of America only ☐ the States indicated in the Supplemental Box

Box No. III FURTHER APPLICANT(S) AND/OR (FURTHER) INVENTOR(S)

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)*

VANDERBIST Francis
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This person is:
☐ applicant only
☒ applicant and inventor
☐ inventor only *(If this check-box is marked, do not fill in below.)*

Applicant's registration No. with the Office

State *(that is, country)* of nationality: BE

State *(that is, country)* of residence: BE

This person is applicant for the purposes of: ☐ all designated States ☐ all designated States except the United States of America ☒ the United States of America only ☐ the States indicated in the Supplemental Box

☒ Further applicants and/or (further) inventors are indicated on a continuation sheet.

Box No. IV AGENT OR COMMON REPRESENTATIVE; OR ADDRESS FOR CORRESPONDENCE

The person identified below is hereby/has been appointed to act on behalf of the applicant(s) before the competent International Authorities as: ☒ agent ☐ common representative

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)*

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Agent's registration No. with the Office

☐ **Address for correspondence:** Mark this check-box where no agent or common representative is/has been appointed and the space above is used instead to indicate a special address to which correspondence should be sent.

Continuation of Box No. III FURTHER APPLICANT(S) AND/OR (FURTHER) INVENTOR(S)

If none of the following sub-boxes is used, this sheet should not be included in the request.

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below:)*

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Belgium

This person is:
- ☐ applicant only
- ☒ applicant and inventor
- ☐ inventor only *(If this check-box is marked, do not fill in below.)*

Applicant's registration No. with the Office

State *(that is, country)* of nationality: FR

State *(that is, country)* of residence: BE

This person is applicant for the purposes of: ☐ all designated States ☐ all designated States except the United States of America ☒ the United States of America only ☐ the States indicated in the Supplemental Box

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)*

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- ☐ applicant only
- ☒ applicant and inventor
- ☐ inventor only *(If this check-box is marked, do not fill in below.)*

Applicant's registration No. with the Office

State *(that is, country)* of nationality: BE

State *(that is, country)* of residence: US

This person is applicant for the purposes of: ☐ all designated States ☐ all designated States except the United States of America ☒ the United States of America only ☐ the States indicated in the Supplemental Box

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)*

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Belgium

This person is:
- ☐ applicant only
- ☐ applicant and inventor
- ☐ inventor only *(If this check-box is marked, do not fill in below.)*

Applicant's registration No. with the Office

State *(that is, country)* of nationality: BE

State *(that is, country)* of residence: BE

This person is applicant for the purposes of: ☐ all designated States ☐ all designated States except the United States of America ☒ the United States of America only ☐ the States indicated in the Supplemental Box

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)*

This person is:
- ☐ applicant only
- ☐ applicant and inventor
- ☐ inventor only *(If this check-box is marked, do not fill in below.)*

Applicant's registration No. with the Office

State *(that is, country)* of nationality:

State *(that is, country)* of residence:

This person is applicant for the purposes of: ☐ all designated States ☐ all designated States except the United States of America ☐ the United States of America only ☐ the States indicated in the Supplemental Box

☐ Further applicants and/or (further) inventors are indicated on another continuation sheet.

Box No. V DESIGNATION OF STATES *Mark the applicable check-boxes below; at least one must be marked.*

The following designations are hereby made under Rule 4.9(a):

Regional Patent

☒ AP ARIPO Patent: GH Ghana, GM Gambia, KE Kenya, LS Lesotho, MW Malawi, MZ Mozambique, SD Sudan, SL Sierra Leone, SZ Swaziland, TZ United Republic of Tanzania, UG Uganda, ZM Zambia, ZW Zimbabwe, and any other State which is a Contracting State of the Harare Protocol and of the PCT *(if other kind of protection or treatment desired, specify on dotted line)* .....

☒ EA Eurasian Patent: AM Armenia, AZ Azerbaijan, BY Belarus, KG Kyrgyzstan, KZ Kazakhstan, MD Republic of Moldova, RU Russian Federation, TJ Tajikistan, TM Turkmenistan, and any other State which is a Contracting State of the Eurasian Patent Convention and of the PCT

☒ EP European Patent: AT Austria, BE Belgium, BG Bulgaria, CH & LI Switzerland and Liechtenstein, CY Cyprus, CZ Czech Republic, DE Germany, DK Denmark, EE Estonia, ES Spain, FI Finland, FR France, GB United Kingdom, GR Greece, HU Hungary, IE Ireland, IT Italy, LU Luxembourg, MC Monaco, NL Netherlands, PT Portugal, RO Romania, SE Sweden, SI Slovenia, SK Slovakia, TR Turkey, and any other State which is a Contracting State of the European Patent Convention and of the PCT

☒ OA OAPI Patent: BF Burkina Faso, BJ Benin, CF Central African Republic, CG Congo, CI Côte d'Ivoire, CM Cameroon, GA Gabon, GN Guinea, GQ Equatorial Guinea, GW Guinea-Bissau, ML Mali, MR Mauritania, NE Niger, SN Senegal, TD Chad, TG Togo, and any other State which is a member State of OAPI and a Contracting State of the PCT *(if other kind of protection or treatment desired, specify on dotted line)* .....

National Patent *(if other kind of protection or treatment desired, specify on dotted line)*:

☒ AE United Arab Emirates	☒ HR Croatia	☒ OM Oman
☒ AG Antigua and Barbuda	☒ HU Hungary	☒ PG Papua New Guinea
☒ AL Albania	☒ ID Indonesia	☒ PH Philippines
☒ AM Armenia	☒ IL Israel	☒ PL Poland
☒ AT Austria	☒ IN India	☒ PT Portugal
☒ AU Australia	☒ IS Iceland	☒ RO Romania
☒ AZ Azerbaijan	☒ JP Japan	☒ RU Russian Federation
☒ BA Bosnia and Herzegovina	☒ KE Kenya	
☒ BB Barbados	☒ KG Kyrgyzstan	☒ SC Seychelles
☒ BG Bulgaria	☒ KP Democratic People's Republic of Korea	☒ SD Sudan
☒ BR Brazil		☒ SE Sweden
☒ BY Belarus	☒ KR Republic of Korea	☒ SG Singapore
☒ BZ Belize	☒ KZ Kazakhstan	☒ SK Slovakia
☒ CA Canada	☒ LC Saint Lucia	☒ SL Sierra Leone
☒ CH & LI Switzerland and Liechtenstein	☒ LK Sri Lanka	☒ SY Syrian Arab Republic
☒ CN China	☒ LR Liberia	☒ TJ Tajikistan
☒ CO Colombia	☒ LS Lesotho	☒ TM Turkmenistan
☒ CR Costa Rica	☒ LT Lithuania	☒ TN Tunisia
☒ CU Cuba	☒ LU Luxembourg	☒ TR Turkey
☒ CZ Czech Republic	☒ LV Latvia	☒ TT Trinidad and Tobago
☒ DE Germany	☒ MA Morocco	
☒ DK Denmark	☒ MD Republic of Moldova	☒ TZ United Republic of Tanzania
☒ DM Dominica		☒ UA Ukraine
☒ DZ Algeria	☒ MG Madagascar	☒ UG Uganda
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☒ EE Estonia		
☒ ES Spain	☒ MN Mongolia	☒ UZ Uzbekistan
☒ FI Finland	☒ MW Malawi	☒ VC Saint Vincent and the Grenadines
☒ GB United Kingdom	☒ MX Mexico	☒ VN Viet Nam
☒ GD Grenada	☒ MZ Mozambique	☒ YU Serbia and Montenegro
☒ GE Georgia	☒ NI Nicaragua	☒ ZA South Africa
☒ GH Ghana	☒ NO Norway	☒ ZM Zambia
☒ GM Gambia	☒ NZ New Zealand	☒ ZW Zimbabwe

Check-boxes below reserved for designating States which have become party to the PCT after issuance of this sheet:

☐ ..... ☐ ..... ☐ .....

Precautionary Designation Statement: In addition to the designations made above, the applicant also makes under Rule 4.9(b) all other designations which would be permitted under the PCT except any designation(s) indicated in the Supplemental Box as being excluded from the scope of this statement. The applicant declares that those additional designations are subject to confirmation and that any designation which is not confirmed before the expiration of 15 months from the priority date is to be regarded as withdrawn by the applicant at the expiration of that time limit. *(Confirmation (including fees) must reach the receiving Office within the 15-month time limit.)*

Supplemental Box *If the Supplemental Box is not used, this sheet should not be included in the request.*

1. *If, in any of the Boxes, except Boxes Nos. VIII(i) to (v) for which a special continuation box is provided, the space is insufficient to furnish all the information: in such case, write "Continuation of Box No...." (indicate the number of the Box) and furnish the information in the same manner as required according to the captions of the Box in which the space was insufficient, in particular:*

   (i) *if more than two persons are to be indicated as applicants and/or inventors and no "continuation sheet" is available: in such case, write "Continuation of Box No. III" and indicate for each additional person the same type of information as required in Box No. III. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below;*

   (ii) *if, in Box No. II or in any of the sub-boxes of Box No. III, the indication "the States indicated in the Supplemental Box" is checked: in such case, write "Continuation of Box No. II" or "Continuation of Box No. III" or "Continuation of Boxes No. II and No. III" (as the case may be), indicate the name of the applicant(s) involved and, next to (each) such name, the State(s) (and/or, where applicable, ARIPO, Eurasian, European or OAPI patent) for the purposes of which the named person is applicant;*

   (iii) *if, in Box No. II or in any of the sub-boxes of Box No. III, the inventor or the inventor/applicant is not inventor for the purposes of all designated States or for the purposes of the United States of America: in such case, write "Continuation of Box No. II" or "Continuation of Box No. III" or "Continuation of Boxes No. II and No. III" (as the case may be), indicate the name of the inventor(s) and, next to (each) such name, the State(s) (and/or, where applicable, ARIPO, Eurasian, European or OAPI patent) for the purposes of which the named person is inventor;*

   (iv) *if, in addition to the agent(s) indicated in Box No. IV, there are further agents: in such case, write "Continuation of Box No. IV" and indicate for each further agent the same type of information as required in Box No. IV;*

   (v) *if, in Box No. V, the name of any State (or OAPI) is accompanied by the indication "patent of addition," or "certificate of addition," or if, in Box No. V, the name of the United States of America is accompanied by an indication "continuation" or "continuation-in-part": in such case, write "Continuation of Box No. V" and the name of each State involved (or OAPI), and after the name of each such State (or OAPI), the number of the parent title or parent application and the date of grant of the parent title or filing of the parent application;*

   (vi) *if, in Box No. VI, there are more than five earlier applications whose priority is claimed: in such case, write "Continuation of Box No. VI" and indicate for each additional earlier application the same type of information as required in Box No. VI.*

2. *If, with regard to the precautionary designation statement contained in Box No. V, the applicant wishes to exclude any State(s) from the scope of that statement: in such case, write "Designation(s) excluded from precautionary designation statement" and indicate the name or two-letter code of each State so excluded.*

further agents : continuation of box IV

F. de Kemmeter and Ph. Overath

Box No. VI PRIORITY CLAIM

The priority of the following earlier application(s) is hereby claimed:

Filing date of earlier application *(day/month/year)*	Number of earlier application	Where earlier application is:		
		national application: country or Member of WTO	regional application:* regional Office	international application: receiving Office
item (1)				
item (2)				
item (3)				
item (4)				
item (5)				

☐ Further priority claims are indicated in the Supplemental Box.

The receiving Office is requested to prepare and transmit to the International Bureau a certified copy of the earlier application(s) *(only if the earlier application was filed with the Office which for the purposes of this international application is the receiving Office)* identified above as:

☐ all items ☐ item (1) ☐ item (2) ☐ item (3) ☐ item (4) ☐ item (5) ☐ other, see Supplemental Box

* *Where the earlier application is an ARIPO application, indicate at least one country party to the Paris Convention for the Protection of Industrial Property or one Member of the World Trade Organization for which that earlier application was filed (Rule 4.10(b)(ii))*: .....

.....

Box No. VII INTERNATIONAL SEARCHING AUTHORITY

Choice of International Searching Authority (ISA) *(if two or more International Searching Authorities are competent to carry out the international search, indicate the Authority chosen; the two-letter code may be used)*:

ISA / .....

Request to use results of earlier search; reference to that search *(if an earlier search has been carried out by or requested from the International Searching Authority)*:

Date *(day/month/year)* Number Country *(or regional Office)*

Box No. VIII DECLARATIONS

The following **declarations** are contained in Boxes Nos. VIII (i) to (v) *(mark the applicable check-boxes below and indicate in the right column the number of each type of declaration)*: Number of declarations

☐ Box No. VIII (i)	Declaration as to the identity of the inventor	:
☐ Box No. VIII (ii)	Declaration as to the applicant's entitlement, as at the international filing date, to apply for and be granted a patent	:
☐ Box No. VIII (iii)	Declaration as to the applicant's entitlement, as at the international filing date, to claim the priority of the earlier application	:
☐ Box No. VIII (iv)	Declaration of inventorship (only for the purposes of the designation of the United States of America)	:
☐ Box No. VIII (v)	Declaration as to non-prejudicial disclosures or exceptions to lack of novelty	:

Box No. IX CHECK LIST; LANGUAGE OF FILING

This international application contains:

(a) in paper form, the following number of sheets:

request (including declaration sheets)	:	6
description (excluding sequence listings and/or tables related thereto)	:	14
claims	:	3
abstract	:	1
drawings	:	
Sub-total number of sheets	:	24
sequence listings	:	
tables related thereto	:	
(for both, actual number of sheets if filed in paper form, whether or not also filed in computer readable form; see (c) below)		
Total number of sheets	:	24

(b) ☐ **only in computer readable form** (Section 801(a)(i))
- (i) ☐ sequence listings
- (ii) ☐ tables related thereto

(c) ☐ **also in computer readable form** (Section 801(a)(ii))
- (i) ☐ sequence listings
- (ii) ☐ tables related thereto

Type and number of carriers (diskette, CD-ROM, CD-R or other) on which are contained the
- ☐ sequence listings: .....
- ☐ tables related thereto: .....

(additional copies to be indicated under items 9(ii) and/or 10(ii), in right column)

This international application is accompanied by the following item(s) *(mark the applicable check-boxes below and indicate in right column the number of each item)*: — Number of items

1. ☒ fee calculation sheet : 1
2. ☐ original separate power of attorney :
3. ☐ original general power of attorney :
4. ☐ copy of general power of attorney; reference number, if any: ..... :
5. ☐ statement explaining lack of signature :
6. ☐ priority document(s) identified in Box No. VI as item(s): ..... :
7. ☐ translation of international application into *(language)*: ..... :
8. ☐ separate indications concerning deposited microorganism or other biological material :
9. ☐ sequence listings in computer readable form *(indicate type and number of carriers)*
   - (i) ☐ copy submitted for the purposes of international search under Rule 13*ter* only (and not as part of the international application) :
   - (ii) ☐ *(only where check-box (b)(i) or (c)(i) is marked in left column)* additional copies including, where applicable, the copy for the purposes of international search under Rule 13*ter* :
   - (iii) ☐ together with relevant statement as to the identity of the copy or copies with the sequence listings mentioned in left column :
10. ☐ tables in computer readable form related to sequence listings *(indicate type and number of carriers)*
    - (i) ☐ copy submitted for the purposes of international search under Section 802(b-*quater*) only (and not as part of the international application) :
    - (ii) ☐ *(only where check-box (b)(ii) or (c)(ii) is marked in left column)* additional copies including, where applicable, the copy for the purposes of international search under Section 802(b-*quater*) :
    - (iii) ☐ together with relevant statement as to the identity of the copy or copies with the tables mentioned in left column :
11. ☐ other *(specify)*: ..... :

Figure of the drawings which should accompany the abstract:

Language of filing of the international application: English

Box No. X SIGNATURE OF APPLICANT, AGENT OR COMMON REPRESENTATIVE

Next to each signature, indicate the name of the person signing and the capacity in which the person signs (if such capacity is not obvious from reading the request).

Brussels, August 5, 2003

Roland Pewis de Tenbossche

Roland Pewis de Tenbossche

For receiving Office use only

1. Date of actual receipt of the purported international application: 05 AOU 2003 (05-08-2003)
2. Drawings: ☐ received: ☒ not received:
3. Corrected date of actual receipt due to later but timely received papers or drawings completing the purported international application:
4. Date of timely receipt of the required corrections under PCT Article 11(2):
5. International Searching Authority (if two or more are competent): ISA /
6. ☐ Transmittal of search copy delayed until search fee is paid

For International Bureau use only

Date of receipt of the record copy by the International Bureau:

NEW SINGLE UNIT PHARMACEUTICAL COMPOSITION COMPRISING A MIXTURE OF A FIBRATE AND AN HOMOCYSTEINE REDUCING AGENT

The present invention relates to a single unit pharmaceutical composition comprising at least a fibrate and at least a homocysteine lowering agent useful to reduce the plasma levels of homocysteine in patients to whom fibrates are administered. The fibrate is selected from the group consisting of fenofibrate, bezafibrate, ciprofibrate. The homocysteine lowering agent is selected from the group consisting of folic acid, vitamin B12, Vitamin B6 and Betaine.

The composition of the present invention may be administered to patients one to four times a day preferably once a day.

Compositions of the present invention are further characterised that the single dosage unit contains amounts of fenofibrate comprised between 25mg and 300mg and amounts of folic acid comprised between 0.1mg and 250mg.

BACKGROUND OF THE INVENTION

Number of studies have shown that the lipid lowering therapy including administration of drugs from the fibrate family is associated with an increase of the plasma concentration of total homocysteine. While more studies are needed that investigate the underlying mechanism responsible for the homocysteine increase, it appears that such increases of homocysteine are associated with increased cardiovascular risks.

The increase of homocysteine in patients is known as hyperhomocysteinemia and can be divided into three classes: Severe (homocysteine plasma concentration > 100µmol/L), moderate (25 to 100µmol/L), or mild (16 to 24µmol/L).

Severe hyperhomocysteinemia is usually caused by a homozygous deficiency of the enzyme cystathionine β-synthase. Affected persons have severe mental retardation, ectopic lens, skeletal abnormalities, and severe premature arterial and venous thrombotic disease.

Mild or moderate hyperhomocysteinemia is found in patients with either hereditary or acquired defects in the homocysteine metabolic pathway. Heterozygous deficiency in cystathionine β-synthase is quite common in the general population, with a frequency of 0.3% to 1.4%. A defect in the remethylation pathway is commonly caused by a thermolabile mutant of the methylene-tetra-hydofolate reductase (MTHFR) enzyme that has approximately 50% of the normal enzyme activity; the homozygous state has a prevalence of 5% in the general population. Common causes of acquired hyperhomocysteinemia are deficiency of dietary cobalamin, folate, or pyridoxine (the essential cofactors for the homocysteine metabolic pathway). A recent prospective study showed that mild hyperhomocysteinemia is quite common in the elderly, despite normal serum vitamin concentrations.

Mild to moderate hyperhomocysteinemia is associated with cerebrovascular disease, coronary artery disease, and peripheral vascular disease in persons younger than 55 years and with carotid artery stenosis in the elderly. It is found in 10% of patients with a first episode of DVT (Deep Vein Thrombosis). In a recent prospective study, a graded relationship was found between elevated plasma homocysteine levels and mortality in patients with coronary artery disease.

Homocysteine is a highly reactive amino acid containing a free sulfhydryl group. It can promote oxidation of low-density lipo-protein (LDL) cholesterol and presumably is toxic to vascular endothelium. It may also inhibit thrombomodulin expression and protein C activation and suppress endothelial heparan sulfate expression, both of these effects lead to hypercoagulability. Recently, homocysteine was shown to enhance the binding of lipoprotein(a), and atherogenic lipoprotein to fibrin, which may provide a link between hyperhomocysteinemia, thrombosis, and premature atherosclerosis. The vascular damage caused by high homocysteine levels leads to arterial and venous thrombosis and, perhaps, accelerated atherosclerosis.

The fibrates pertain to the lipid lowering family drugs.

The lipid-modifying effects of fibrate are mediated via the activation of the peroxisome proliferator-activated receptors (PPARs).

Fibrates reduce plasma total cholesterol (TC), low-density lipoprotein cholesterol (LDL-C), triglyceride (TG) and very-low-density lipoprotein (VLDL) cholesterol levels, and increase high-density lipoprotein cholesterol (HDL-C) and apolipoprotein (Apo) AI and Apo AII levels in patients with dyslipidaemia. Fibrates also reduce plasma fibrinogen levels in both normolipidemic individuals and those with dyslipidemia, and is significantly more effective in that reduction than Simvastatin, Atorvastatin or Pravastatin. This is of significance since increased levels of fibrinogen or

plasminogen activator inhibitor (PAI-1) are associated with an increased risk of atherosclerosis and coronary heart disease (CHD).

Fibrates have also demonstrated a very important activity in reducing the levels of the inflammatory marker C reactive protein (CRP). Which has been recognized to have a negative effect on the evolution of the pathogenesis of atherosclerosis and coronary heart diseases.

Fibrates of interest for the present invention include but are not limited to: Fenofibrate, Bezafibrate and Ciprofibrate..

Fenofibrate or p-(4-chlorobenzoyl)-phenoxy isobutyrate isopropyl ester is useful for the treatment of adult patients with very high elevations of serum triglyceride levels and/or cholesterol levels. The usual daily dosage is 50 to 300mg which is administered in one or two doses. Fenofibrate absorbed as fenofibric acid, resulting from the hydrolysis of fenofibrate, is extensively bound to plasma albumin. The plasma half-life is about 20 hours. Fenofibric acid is excreted predominantly in the urine, mainly as the glucuronide conjugate, but also as a reduced form of fenofibric acid and its glucuronides.

Bezafibrate or α-[4-(4-chlorobenzoylaminoethyl)phenoxy]isobutyric acid is rapidly absorbed when taken via the oral route, with a plasma peak concentration at 1-2 hours. The bioavailability of bezafibrate is close to 100%. The elimination half-life is 2.1 hours. Bezafibrate is highly bound to plasmatic proteins (95%). Bezafibrate is eliminated either unchanged in the urine or under the form of a glucuron conjugate metabolite and other metabolites.

Ciprofibrate or 2-[4-(2,2-dichlorocydopropyl)phenoxy]isobutyric acid is rapidly absorbed. After oral intake, the plasma peak concentration is reached, after 1 to 4 hours. Ciprofibrate is highly bound to plasmatic proteins (97%). Its elimination half-life is long from 38 to 86 hours. 30 to

75% of ciprofibrate is found in the urine under the form of a glucuron conjugate metabolite.

While some study results seem to be contradictory. It is now, commonly admitted by the medical community that, Fenofibrate, Bezafibrate and Ciprofibrate administration to patient increases the level of homocysteine. (Drug Safety 2003:26(2) 81-91).

The effect of Fenofibrate, compared with Placebo on total plasma homocysteine levels in the fasted and the fed states has been examined. Fenofibrate caused marked decrease in all triglyceride rich protein parameters and was associated with an increase in fasting total homocysteine, from 10.3µmol/L to 14.4µmol/L (+40%) and fed total homocysteine levels 6 hours past prandil load from 11.6µmol/L t0 17.1µmol/L [Atherosclerosis.2001 Apr:155(2): 455-62).

A homocysteine lowering agent is defined as a substance able to decrease plasma levels of homocysteine in humans in such a need. Examples of those homocysteine lowering agents are: Folic acid, vitamin B6, vitamin B12 and Betaine.

Also it has been shown that in patient not receiving lipid-lowering drugs, vitamin supplementation with folic acid and vitamin B12 effectively reduces the plasma homocysteine levels.

Also, while some studies have shown that folic acid or vitamin combination to Fenofibrate could allow to decrease the homocysteine increase associated with the Fenofibrate administration. These studies were performed alternately (one day fibrate and one day vitamin) or by administration of folic acid, vitamin B6 and/or B12 upon completion of the fibrate treatment.

What was never disclosed, nor suggested is an oral single unit pharmaceutical composition consisting of the combination of a therapeutic

effective amount of fibrate derivative with at least an effective amount of lowering homocysteine agent or a mixture of such lowering homocysteine agents. A single unit form is a pharmaceutical form containing both the fibrate derivative and the homocysteine lowering agent in such a way that the patient can swallow the said pharmaceutical form in a single intake.

Also, all the previous art was directed towards reducing the levels of homocysteine after they were first increased while an object of the present invention is to provide for a pharmaceutical composition that avoids the increase of homocysteine in the patient. In other words, the present invention relates to a pharmaceutical composition containing a fibrate and able, to some extent, to prevent the increase of homocysteine plasma levels caused by the fibrate.

It is an object of the present invention to provide an orally administered pharmaceutical composition of a fibrate and an homocysteine lowering agent that provides for a therapeutically effective amount of the fibrate and that substantially reduces the increase of plasma homocysteine otherwise encountered after administration of such amount of fibrate to the patient.

It is another object of the present invention to provide an orally administered pharmaceutical composition of a fibrate and an homocysteine lowering agent which is contained into a single unit formulation.

It is another object of the present invention to provide an orally administered pharmaceutical composition of a fibrate and a homocysteine lowering agent which is suitable for once or twice a day administration preferably for once a day administration.

It is another object of the present invention to provide an orally administered pharmaceutical composition of a fibrate and a homocysteine lowering agent, from which the release of one or more of the active ingredient is immediate, delayed, extended or any combination for thereof.

It is another object of the present invention to provide an orally administered pharmaceutical composition of a fibrate and an homocysteine lowering agent which comprises a fibrate selected from the group comprising Fenofibrate, Bezafibrate or Ciprofibrate.

It is another object of the present invention to provide an orally administered pharmaceutical composition of a fibrate and a homocysteine lowering agent which comprises a homocysteine lowering agent selected from the group comprising folic acid, vitamin B6, vitamin B12, betaine alone or in mixtures thereof.

It is another object of the present invention to provide a method of treatment of hypercholesterolemia and related diseases of dyslipidemia comprising the administration of the dosage forms of the composition of the present invention to a patient in need of treatment.

Details and advantageous characteristics of compositions of the invention are given in the attached claims.

DETAILED DESCRIPTION OF THE INVENTION

Different pharmaceutical formulations may be used to obtain the single unit form of the present invention. For instance, a capsule containing a coated or uncoated tablet of homocysteine lowering agent with a semi-solid composition of fenofibrate is suitable.

Other alternatives are capsules containing homocysteine lowering agent under the form of powder, pellets or tablets and fenofibrate formulated as paste, semi-solid tablet, granulated powder or pellets, coated or uncoated tablets, but always combined in a single unit form.

Also a modified release form of homocysteine lowering agent release is acceptable such as an enteric tablet or capsule, a sustained release form (tablet or granules) or a form combining an immediate release form of the

homocysteine lowering agent with a prolonged release form of the same homocysteine lowering agent.

As fibrate derivatives usually present a relatively long elimination half-life, from 20 to 90 hours (with the exception of bezafibrate which presents a elimination half-life of 2.1 hours), and some of vitamin B derivatives present a short half-life (folic acid : 3 hours), it is a particularly interesting object of the present invention to provide a composition where the fibrate is formulated as an immediate release form and the vitamin B derivative at least partly as a sustained or delayed release formulation (both derivatives being finally put into a single unit form) in order to optimize the duration of action of the vitamin B derivative and to increase as much as possible its therapeutic homocysteine lowering effect.

For instance, the single unit final form can be a capsule containing a semi-solid formulation of fibrate derivative, preferably fenofibrate, and a sustained release tablet (coated or not) containing the vitamin B derivative.

Examples of such sustained release vitamin B formulations can be matrix tablets containing an hydrophilic or an hydrophobic polymer (or a mixture thereof), sustained release coated granules, matrix granules, etc,...

When formulating sustained release compositions of vitamins B derivatives, the absorption window should be taken into account. For instance, folic acid has its main absorption window in the proximal jejunum. The sustained release of folic acid should therefore not be too slow because it should be delivered completely within the absorption window. For instance, such sustained release formulations of folic acid should present a Tmax in vivo of between 1 and 10 hours, preferably between 2 and 8 hours, more preferably between 2 and 6 hours. When tested in vitro, on a paddle dissolution apparatus (EP 2003, 4th edition, 2.9.3) at 100 round per minute (rpm), the dissolution rate is for instance of 5 to 70 % dissolved after 1 hour, 20 to 90 % dissolved after 2 hours, 50-95 % dissolved after 4 hours and more than 80 % dissolved after 8 hours.

Alternatively the homocysteine lowering agent can be a combination of various homocysteine lowering agents such as, but not limited to, a combination of folic acid and vitamin B12 or a combination of folic acid and vitamin B6 or even a combination of folic acid with vitamin B12 and vitamin B6.

Examples

The invention is additionally illustrated in connection with the following examples, which are considered to be illustrative of the present invention. It should be understood, however, that the invention is not limited to the specific details of the Examples.

Example 1

Ingredient Name	**Amount [g]**
folic acid	1
Lactose monohydrate	100
Cellulose microcrystalline	36
Povidone K30	2
Water for granulation	25
Magnesium stearate	2
Sodium starch glycolate	13

Folic acid, lactose monohydrate, cellulose microcrystalline and povidone K30 were blended in a planetary mixer for about 5 to 10 minutes until an homogeneous blend was obtained. While under agitation, a solution containing the water for granulation was added to granulate the powders. The granules obtained were dried at about 40°C for about 5 hours. Thereafter the dried granules were screened through a 1.0 mm sieve, and further blended into a planetary mixer for about 2 minutes after the addition of the magnesium stearate and sodium starch glycolate.

The final mix was compressed into tablets using a rotary compressing machine equipped with punches of the deep cup type with a diameter of 6.5mm. The mean weight of the tablets was 180 mg, corresponding to tablets containing 1 mg of folic acid. The tablet hardness was comprised between 4 and 6 kilopascals (Kp).

Example 2

Ingredient Name	**Amount [g]**
Povidone K30	35
Talc	35
Triacetin	5
Absolute Alcohol	300

This coating solution was applied to the tablets from Example 1 using a pan coater. The amount of coating applied was about 14.4 mg of dry coating (weight gain) per tablet.

Example 3

Ingredient Name	**Amount [g]**
Fenofibrate powder	160
Lauroyl macrogolglyceride (gelucire 44/14)	240
Polyethylene glycol 20,000	48
Hydroxypropylcellulose	95.0
Sodium starch glycolate	20.0
Ascorbyl palmitate	1.0

Gelucire 44/14 and polyethylene glycol 20,000 were added to a mixer equipped with a double wall bowl. The mixer was started and the bowl was warmed at about 75°C. When the gelucire and the polyethylene glycols

were molten, the other ingredients (Fenofibrate, hydroxypropyl cellulose, sodium starch glycolate and ascorbyl palmitate) were added while maintaining the temperature at about 70 - 75°C.

Example 4

The combination product was obtained by filling, into size 0 elongated hard gelatin capsules, one tablet of Example 2 and 564mg of the hot blend of Example 3. After filling, the capsules were cooled by placing them on trays between 4 and 8°C.

The capsules obtained contained 1 mg of folic acid and 160mg of fenofibrate.

Example 5

Ingredient Name	**Amount [g]**
folic acid	2
vitamin B12	0.5
EUDRAGIT® NE30D	10
Lactose monohydrate	100
Cellulose microcristalline	40
Povidone K30	2
Water for granulation	30
Magnesium stearate	2
Sodium starch glycolate	13

Folic acid, Vitamin B12, Lactose monohydrate, cellulose microcrystalline and povidone K30 were blended in a planetary mixer for about 5 to 10 minutes until an homogeneous blend was obtained. While under agitation, an aqueous suspension of EUDRAGIT® NE30D (polyacrylate dispersion 30 %) into the water for granulation was added to granulate the powders. The granules obtained were dried at about 40°C for about 5 hours. After the

dried granules were screened through a 1.0 mm sieve, they were blended into a planetary mixer for about 2 minutes after the addition of the magnesium stearate and sodium starch glycolate. The final mix was compressed into tablets using a rotary compressing machine equipped with punches of the deep cup type with a diameter of 6.5mm. The mean weight of the tablets was 200 mg. The tablets had hardness comprised between 4 and 6 kilopascals (Kp). It should be noted that the matrix tablet obtained allow to deliver folic acid in a sustained release manner.

These core tablets were coated with the coating solution and the coating method parameters of Example 2.

Example 6

Ingredient	**Amount [g]**
Fenofibrate powder	160
Lactose	300
Povidone K30	15
Sodium Lauryl Sulfate	7
Crospovidone	15
Magnesium Stearate	3

Fenofibrate, lactose, povidone and sodium lauryl sulfate were blended in a planetary mixer and water was added to granulate. After oven drying for about 5 hours at 50°C, the granules were screened through a 1mm sieve. After addition of crospovidone and the magnesium stearate the granules that were blended for an additional 3 minutes in the planetary mixer.

Example 7

500 mg of lubricated granules of Example 6 and a tablet of Example 5 were filled into 0 elongated hydroxypropylmethylcellulose capsules to produce a combination product containing 2 mg of folic acid, 0.5 mg of vitamin B12 and 160mg of fenofibrate.

Example 8

Ingredient Name	Amount [g]
Folic acid	5
sucroester (Crodesta®)	20
Microcrystalline cellulose	100
Povidone K30	20
	145

To the blend of all the ingredients in a planetary mixer was added water to granulate. The paste obtained was extruded and spheronized in order to obtain beads with a diameter of about 1mm. The beads were tray dried in an oven at about 40°C for approximately 5 hours. The beads were thereafter screened between 0.7mm and 1.4mm sieves.

Example 9

500 g of beads from Example 8 were coated with 200 g of coating solution (which are equal to 40 g of dry residue) of Example 2 using a fluid bed coater (Strea 1) equipped with a wurster column.

Example 10

A combination formulation was produced by filling 0 elongated hard gelatin capsules with 500 mg of Fenofibrate lubricated granules of Example 6 and 145 mg of folic acid beads of Example 8.

The resulting combination formulation contained 5 mg of folic acid and 160mg of fenofibrate.

WHAT WE CLAIM IS :

1. An oral lipid lowering pharmaceutical unit form comprising a first solid or semi solid composition comprising a fibrate derivative and a second solid or semi solid composition comprising at least a homocysteine lowering agent.

2. The pharmaceutical composition according to claim 1 characterised that it comprises an effective amount of fibrate derivative for the treatment of hyperlipidemia.

3. The pharmaceutical composition according to claim 1 in which the fibrate derivative is selected from the group consisting of Fenofibrate, Bezafibrate , Ciprofibrate and mixtures thereof.

4. The pharmaceutical composition according to claim 1, in which the homocysteine lowering agent is selected from the group consisting of folic acid, vitamin B12, vitamin B6, Betaine, and mixtures thereof.

5. The pharmaceutical composition according to claim 1, in which the amount of Fenofibrate is comprised between 25mg and 400mg, preferably between 50mg and 300mg.

6. The pharmaceutical composition according to claim 5 in which the Fenofibrate is present under the form of micronized Fenofibrate.

7. The pharmaceutical composition according to claim 1 in which the Fenofibrate is present in mixture with at least one polyglyceride.

8. The pharmaceutical composition according to claim 1 from which the release of the homocysteine lowering agent is immediate, delayed, extended or any combination of these releases.

9. The pharmaceutical composition according to claim 1 wherein the fibrate derivative is fenofibrate and the homocysteine lowering agent is folic acid.

10. The pharmaceutical composition of claim 1, in which the first composition is an substantially immediate release composition of the fibrate derivative.

11. The Pharmaceutical composition of claim 10, in which the fibrate derivative is released substantially completely in less than about 3.0 hour according to the paddle method.

12. The pharmaceutical composition according to claim 1, wherein the dose of fenofibrate is between 50 and 300 mg and the dose of folic acid is between 0.1 and 100 mg.

13. The pharmaceutical composition according to claim 1 where the single unit form is a hard gelatin, hypromellose capsule or any other pharmaceutically acceptable capsule.

14. The pharmaceutical composition according to claim 1 where the single unit form is a tablet.

15. The pharmaceutical composition according to claim 1 wherein folic acid is an immediate release form.

16. The pharmaceutical composition according to claim 1 wherein folic acid is a modified release form.

17. The pharmaceutical composition according to claim 1 wherein the second composition is a composition combining an immediate release form of a part of the homocysteine lowering agent with a prolonged release form of another part of the homocysteine lowering agent.

18. The pharmaceutical composition according to claim 1, in which the second composition is a composition controlling the release of the homocysteine lowering agent so as to ensure a Tmax (time for reaching the maximum peak concentration in the human plasma) in vivo of between 1 and 10 hours, preferably between 2 and 8 hours, more preferably between 2 and 6 hours.

19. The pharmaceutical composition according to claim 1, in which the second composition is a composition controlling the release of the homocysteine lowering agent so as to ensure a dissolution rate in vitro, on a paddle dissolution apparatus (EP 2003, 4th edition, 2.9.3) at 100 round per minute (rpm), of 5 to 70 % after 1 hour, 20 to 90 % after 2 hours, 50-95 % after 4 hours and more than 80 % after 8 hours.

20. The pharmaceutical composition according to claim 1 wherein the homocysteine lowering agent is a mix of two or more of said substances.

21. The pharmaceutical composition according to claim 1, wherein the final form is a capsule containing fenofibrate as a paste and folic acid as coated or uncoated immediate or sustained release tablet.

22. The pharmaceutical composition according to claim 1, wherein the first solid or semi solid composition comprising a fibrate derivative is substantially free of homocysteine lowering agent and/or the second solid or semi solid composition comprising at least a homocysteine lowering agent is substantially free of fibrate derivative.

Abstract

NEW SINGLE UNIT PHARMACEUTICAL COMPOSITION COMPRISING A MIXTURE OF A FIBRATE AND AN HOMOCYSTEINE REDUCING AGENT

An oral lipid lowering pharmaceutical unit form comprising a first solid or semi solid composition comprising a fibrate derivative and a second solid or semi solid composition comprising at least a homocysteine lowering agent.